United States Patent Application for:

RECEPTACLE FOR AN AEROSOLIZABLE PHARMACEUTICAL FORMULATION

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Docket No.:	0136.PRO

CERTIFICATE OF EXPRESS MAILING:

"Express Mail" mailing label number ER212309934 Date of Deposit December 5, 2003

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Receptacle For an Aerosolizable Pharmaceutical Formulation

This application claims the benefit U.S. Provisional Patent Application Serial No. 60/437,254 filed on December 31, 2002, which is incorporated herein by reference in its entirety.

BACKGROUND

The need for effective therapeutic treatment of patients has resulted in the development of a variety of pharmaceutical formulation delivery techniques. One traditional technique involves the oral delivery of a pharmaceutical formulation in the form of a pill, capsule, elixir, or the like. However, oral delivery can in some cases be undesirable. For example, many pharmaceutical formulations may be degraded in the digestive tract before they can be effectively absorbed by the body. Inhaleable drug delivery, where an aerosolized pharmaceutical formulation is orally or nasally inhaled by a patient to deliver the formulation to the patient's respiratory tract, has proven to be a particularly effective and/or desirable alternative. For example, in one inhalation technique, an aerosolized pharmaceutical formulation provides local therapeutic relief to a portion of the respiratory tract, such as the lungs, to treat diseases such as asthma, emphysema, and cystic fibrosis. In another inhalation technique, a pharmaceutical formulation is delivered deep within a patient's lungs where it may be absorbed into the blood stream. Many types of inhalation devices exist including devices that aerosolize a dry powder pharmaceutical formulation.

One type of inhalation device aerosolizes a pharmaceutical formulation that is stored in a capsule. For example, a dose or a portion of a dose of a dry powder pharmaceutical formulation may be stored in a capsule, and the capsule may be inserted into an aerosolization device which is capable of aerosolizing the pharmaceutical formulation. After being inserted into the aerosolization device, the capsule is opened to expose the pharmaceutical formulation. The opening of the capsule may be performed, for example, by puncturing or tearing the capsule. When the capsule is properly opened and when aerosolization energy is supplied, the pharmaceutical formulation is aerosolized so that it may be inhaled by the user and a dose or portion of a dose of the aerosolized pharmaceutical formulation may be delivered to the user's respiratory tract.

However, improper use of the aerosolization device may result in the delivery of less than the desired amount of the pharmaceutical formulation. For example, if a capsule is not properly or completely opened before the aerosolization process, the amount of pharmaceutical formulation being aerosolized may be reduced or the flow of the aerosolized pharmaceutical formulation may not be of sufficiently high quality to deliver a desirable amount to the user. This improper opening is particularly prevalent when a user is unable or unwilling to visually inspect the opening of the capsule. The user may then unknowingly inhale less than a desired amount of the pharmaceutical formulation. In addition, sharpened elements for creating the opening in the capsule may produce inconsistent openings into the capsule which can result in inconsistent delivery of aerosolized medicament.

Therefore, it is desirable to be able to provide a receptacle for an aerosolizable pharmaceutical formulation that is readily and consistently openable. It is further desirable to be able to provide such opening without the use of sharpened elements.

SUMMARY

The present invention satisfies these needs. In one aspect of the invention, a receptacle is openable without using a sharpened tip.

In another aspect of the invention, an aerosolization system comprises an aerosolization device comprising a chamber adapted to receive a receptacle. The aerosolization system also comprises a receptacle containing a pharmaceutical formulation, the receptacle comprising a wall having a weakened portion that opens when a force is applied. An opening into the receptacle may be created at the weakened portion before, during, or after insertion of the receptacle into the chamber by applying a force to the receptacle.

In another aspect of the invention, a method of aerosolizing a pharmaceutical formulation comprises providing an aerosolization device comprising a chamber; providing a receptacle containing a pharmaceutical formulation, the receptacle comprising a wall having a weakened portion that opens when a force is applied; applying a force to the receptacle to create an

opening at the weakened portion; before, during, or after applying the force to the receptacle, inserting the receptacle into the chamber; and aerosolizing the pharmaceutical formulation in the chamber.

In another aspect of the invention, a receptacle is provided for use in an aerosolization device comprising a chamber adapted to receive the receptacle. The receptacle comprises a wall having a weakened portion that opens when a force is applied and a pharmaceutical formulation within the wall, whereby an opening may be created at the weakened portion before, during, or after insertion of the receptacle into the chamber by applying a force to the receptacle.

DRAWINGS

These features, aspects, and advantages of the present invention will become better understood with regard to the following description, appended claims, and accompanying drawings which illustrate exemplary features of the invention. However, it is to be understood that each of the features can be used in the invention in general, not merely in the context of the particular drawings, and the invention includes any combination of these features, where:

Figure 1A is a schematic sectional side view of an aerosolization apparatus and receptacle in an initial position;

Figure 1B is a schematic sectional side view of the aerosolization apparatus and receptacle shown in Figure 1A at the beginning a receptacle opening process;

Figure 1C is a schematic sectional side view of the aerosolization apparatus and receptacle shown in Figure 1A during the a receptacle opening process;

Figure 1D is a schematic sectional side view of the aerosolization apparatus and receptacle shown in Figure 1A during the beginning of an aerosolization process;

Figure 1E is a schematic sectional side view of the aerosolization apparatus and receptacle shown in Figure 1A during the aerosolization process;

Figures 2A and 2B are schematic perspective views of a version of a receptacle according to the invention in an unopened and an opened condition, respectively;

Figures 3A through 3E are schematic sectional side views of a receptacle opening and aerosolization process using a receptacle according to the invention in another version of an aerosolization apparatus;

Figures 4A and 4B are schematic perspective views of another version of a receptacle according to the invention in an unopened and an opened condition, respectively;

Figures 5A through 5C are schematic sectional side views showing a receptacle according to the invention being opened by another version of an opening mechanism;

Figures 6A through 6C are schematic sectional side views showing a receptacle according to the invention being used in a version of an aerosolization apparatus which includes an opening mechanism with a flexible side wall;

Figures 7A and 7B are schematic perspective views of another version of a receptacle according to the invention in an unopened and an opened condition, respectively;

Figures 8A and 8B are schematic perspective views of another version of a receptacle according to the invention in an unopened and an opened condition, respectively;

Figure 9A is a schematic perspective views of an elongated portion of another version of a receptacle according to the invention in an unopened condition;

Figure 9B is a schematic sectional view of the elongated portion of Figure 9A in a stressed and in an unstressed condition;

Figure 10A is a schematic perspective views of an elongated portion of another version of a receptacle according to the invention in an unopened condition;

Figure 10B is a schematic sectional view of the elongated portion of Figure 10A in a stressed and in an unstressed condition.

DESCRIPTION

The present invention relates to a receptacle for storing a pharmaceutical formulation. Although the process is illustrated in the context of storing an aerosolozable dry powder pharmaceutical formulation in a receptacle, the present invention can be used in other processes and should not be limited to the examples provided herein.

An aerosolization apparatus **100** and pharmaceutical formulation receptacle **125** according to the present invention is shown schematically in Figure 1A. The aerosolization apparatus **100** comprises a housing **105** defining a chamber **110** having one or more air inlets **115** and one or more air outlets **120**. The chamber **110** is sized to receive a receptacle **125** which contains an aerosolizable pharmaceutical formulation. An opening mechanism **130** comprises an opening member **135** that is moveable within the chamber **110**. Near or adjacent the outlet **120** is an end section **140** that may be sized and shaped to be received in a user's mouth or nose so that the user may inhale through an opening **145** in the end section **140** that is in communication with the outlet **120**.

The aerosolization apparatus **100** utilizes air flowing through the chamber **110** to aerosolize the pharmaceutical formulation in the receptacle **125**. For example, Figures 1A through 1E illustrate the operation of a version of an aerosolization apparatus **100** where air flowing through the inlet **115** is used to aerosolize the pharmaceutical formulation and the aerosolized pharmaceutical formulation flows through the outlet **120** so that it may be delivered to the user through the opening **145** in the end section **140**. The aerosolization apparatus **100** is shown in its

initial condition in Figure 1A. The receptacle **125** is positioned within the chamber **110** and the pharmaceutical formulation is contained within the receptacle **125**.

To use the aerosolization apparatus **100**, the pharmaceutical formulation in the receptacle **125** is exposed to allow it to be aerosolized. In the version of Figures 1A though 1E, the opening mechanism **130** is advanced within the chamber **110** by applying a force **150** to the opening mechanism **130**. For example, a user may press against a surface **155** of the opening mechanism **130** to cause the opening mechanism **130** to slide within the housing **105** so that the opening member **135** contacts the receptacle **125** in the chamber **110**, as shown in Figure 1B. By continuing to apply the force **150**, the opening member **135** is advanced to abut the forward wall **122** of the receptacle **125**, as shown in Figure 1C. The opening member may comprise one or more blunt tips **152** that contact the receptacle **125** in a manner that provides an opening into the receptacle **125**. The opening mechanism **130** is then retracted to the position shown in Figure 1D, leaving an opening **160** through the wall of the receptacle **125** to expose the pharmaceutical formulation in the receptacle **125**.

Air or other gas then flows through an inlet **115**, as shown by arrows **165** in Figure 1E. The flow of air causes the pharmaceutical formulation to be aerosolized. When the user inhales **170** through the end section **140** the aerosolized pharmaceutical formulation is delivered to the user's respiratory tract. In one version, the air flow **165** may be caused by the user's inhalation **170**. In another version, compressed air or other gas may be ejected into the inlet **115** to cause the aerosolizing air flow **165**.

Proper creation of the opening **160** in the receptacle **125** allows for efficient and effective delivery of the aerosolized pharmaceutical formulation to the user. In contrast, improper creation of the opening **160** can lead to inefficient and less effective delivery of the medicament to a user. Accordingly, in one version, the receptacle **125** is designed to be at least partially self-opening when force is applied thereto. For example, as shown in Figure 2A, the receptacle **125** may comprise a wall **299** having a weakened portion **300** that opens when a force is applied, such as a non-puncturing force. The weakened portion **300** comprises a region of the wall altered so as to fracture at a force less than would be necessary without the alteration. The alteration is added for

the purpose of lessening the required fracture force and/or for the purpose of controlling the fracture. In one version, the weakened portion **300** comprises one or more scored or otherwise weakened lines **305**. When a blunt force, such as a force from tip **152**, is applied to the weakened portion **300**, the lines **305** break and an opening **160** is created, as shown in Figure 2B.

Another version of an aerosolization apparatus **100** comprising a blunt opening member **135** having a plurality of tips **152** for opening a receptacle **125** with a plurality of weakened portions **300** is shown in Figures 3A through 3E. In this version, the housing **105** of the aerosolization apparatus **100** comprises a body **205** and a removable endpiece **210**. The endpiece **210** may be removed from the body **205** to insert a receptacle **125** in the chamber **110** which is formed when the body **205** and the endpiece **210** are connected together. The endpiece **210** comprises a partition **215** that blocks the forward end of the chamber **110**, and the partition **215** has the one or more outlets **120** extending therethrough. An example of an aerosolization apparatus with a partition **215** and chamber **110** are described in U.S. Patent 4,069,819 and in U.S. Patent 4,995,385, both of which are incorporated herein by reference in their entireties. In such an arrangement, the chamber **110** comprises a longitudinal axis that lies generally in the inhalation direction, and the receptacle **125** is insertable lengthwise into the chamber **110** so that the receptacle's longitudinal axis may be parallel to the longitudinal axis of the chamber **110**. In the version of Figures 3A through 3E, the chamber **110** is sized to receive a receptacle **125** containing a pharmaceutical formulation in a manner which allows the receptacle to move within the chamber **110**. The inlets **115** comprise a plurality of tangentially oriented slots **220**. When a user inhales **170** through the endpiece **210**, outside air is caused to flow through the tangential slots **220** as shown by arrows **225** in Figure 3E. This airflow **225** creates a swirling airflow within the chamber **110**. The swirling airflow causes the receptacle **125** to contact the partition **215** and then to move within the chamber **110** in a manner that causes the pharmaceutical formulation to exit the receptacle **125** and become entrained within the swirling airflow. In one version, the receptacle **125** may rotate within the chamber **110** in a manner where the longitudinal axis of the receptacle, which may be a capsule, remains at an angle less than 80 degrees, and preferably less than 45 degrees from the longitudinal axis of the chamber. The movement of the receptacle **125** in the chamber **110** may be caused by the width of the chamber **110** being less than the length of the receptacle **125**. In one specific version, the chamber **110** comprises a tapered section **230** that terminates at an edge

235. During the flow of swirling air in the chamber **110**, the forward end of the receptacle **125** contacts and rests on the partition **215** and a sidewall of the receptacle **125** contacts the edge **235** and slides and/or rotates along the edge **235**. This motion of the receptacle, which may be a capsule, is particularly effective in forcing a large amount of the pharmaceutical formulation through the plurality of openings **160** in the rear of the receptacle **125**.

The plurality of openings **160** in the rear of the receptacle **125** in the version of Figures 3A through 3E are created by an opening mechanism **130** that is slidable within the body **205**. The opening mechanism **130**, shown in its rest position in Figure 3A, comprises a plunger **240** attached at its forward end **245** to the opening member **135**, which in the version shown is a U-shaped staple **250** having a plurality of blunt tips **152**, such as the two tips shown in this version. The opening mechanism **130** further comprises a seating member **255** which contacts the plunger **240** and/or the opening member **135** and is slidable relative to the plunger **240** and the opening member **135**. To create the openings **160** in the receptacle **125**, the user applies a force **150** to the plunger **240**, as shown in Figure 3B, such as by pressing against the end surface **155** of the plunger **240** with the user's finger or thumb. The force **150** causes the plunger to slide within the body **205**. A slight frictional contact between the plunger **240** the a rear section **260** of the seating member **255** causes the seating member **255** to also slide within the body **205** until a forward seating surface **265** of the seating member **255** contacts the receptacle **125**, as shown in Figure 3B. The forward seating surface **265**, which may be shaped to generally match the shape of the receptacle **125**, secures the receptacle **125** between the seating member **255** and the partition **215**. The continued application of force **150** causes the plunger **240** and the opening member **135** to slide relative to the seating member **255**, as shown in Figure 3C, to advance the opening member **135** through openings **270** in the forward seating surface **265** and to the receptacle **125** to create the openings **160** as discussed above. Upon the removal of the force **150**, a spring **275** or other biasing member urges the opening mechanism **130** back to its rest position. For example, the spring **275** may contact a shoulder **280** in the body **205** and press a flange **285** on the plunger **240** toward a rim **290** in the body **205**. The frictional engagement between the plunger **240** and the seating member **255** also returns the seating member **255** to its retracted position when the plunger is returned to its retracted position.

A receptacle **125** that may be used with the aerosolization apparatus **100** of Figures 3A through 3E is shown in Figures 4A and 4B. The receptacle **125** of Figure 4A comprises a plurality of weakened portions **300**, each of which is contacted by a blunt tip **152** of the aerosolization apparatus **100** to create the plurality of openings **160**, as shown in Figure 4B.

Figures 5A through 5C demonstrate another type of an opening mechanism **130** that may be used to create one or more openings in a receptacle **125**. In this version, a receptacle **125** having one or more weakened portions **300** is placed in a chamber **110** having one or more flexible sidewalls **320**. To create an opening **160** into the receptacle **125**, a user applies a force **325** to one or more of the flexible sidewalls **320** to cause a flexible sidewall **320** to contact a weakened portion **300** of the receptacle **125**, as shown in Figure 5B. The force against the weakened portion **300** creates the one or more openings **160** illustrated in Figure 5C. The flexible sidewall **320** may be biased to its extended position so that it returns to the configuration shown in Figure 5C when the force **325** is removed. The opening mechanism **130** of this version or of any other version may either be included within the aerosolization apparatus **100** or may be separate from the apparatus so that the receptacle may be opened before, during or after being inserted into the aerosolization apparatus **100**.

Another version of an aerosolization apparatus **100** having an opening mechanism **130** is shown in Figures 6A through 6C. In this version, a flexible wall **320** of the chamber **110** is forced by a user to cause the flexible sidewall **320** to contact a portion of the receptacle **125** other than the weakened portion **300**. The stress on the receptacle **125** causes the weakened portion **300** to fracture to create the one or more openings **160**. For example, the flexible sidewall **320** may contact an elongated portion **325** of the receptacle **125** to cause a weakened portion **300** in an end of the receptacle **125** to fracture.

In another version, the weakened portion **300** of a receptacle **125** may be along an elongated portion **325** of the receptacle **125**, as shown in Figure 7A. For example, the elongated portion **325** may comprises one or more weakened lines **305** that extend along the elongated portion **325**. When a force is applied to the receptacle **125**, the weakened portion **300** opens as shown in Figure 7B. In one version, the receptacle **125** of Figure 7A may be inserted into a chamber **110**

such as the chamber **110** of the version of Figures 5A through 5C. The contacting of the ends of the receptacle **125** causes the openings **160** of Figure 7B to be created. Figures 8A and 8B show different designs of the receptacle **125**.

In one version, the receptacle **125** of Figures 7A and 7B may be designed to be opened in the absence of an opening mechanism **130**. For example, by inserting the receptacle **125** of Figure 7A and 7B into a swirling airflow chamber, such as the chamber described above in connection with Figures 3A through 3E, the rotation of the receptacle **125** during the aerosolization process generates a sufficient force to cause the receptacle to open to the configuration shown in Figure 7B. This allows the aerosolization apparatus **100** to be manufactured in a much simpler manner. Similarly, the versions of Figures 8A and 8B may be opened without the need for an opening mechanism.

Specific designs of an elongated portion **320** of a receptacle **125** having a weakened portion **300** along the elongate portion **320** are shown in Figures 9A and 9B and in Figures 10A and 10B. Figures 9B and 10B show cross sections through the elongate portions **320** of Figures 9A and 10A, respectively, in an unstressed state **340** and in a stressed state **345**. These versions are particularly effective when opened by the aerosolization forces instead of an opening mechanism.

In another version, the aerosolization apparatus **100** may be configured differently than as shown in Figures 1A through 1E and 3A through 3E. For example, the chamber **100** may be sized and shaped to receive the receptacle **125** so that the receptacle **125** is orthogonal to the inhalation direction, as described in U.S. Patent 3,991,761. As also described in U.S. Patent 3,991,761, the opening mechanism **130** may contact both ends of the receptacle **125**. In another version, the chamber may receive the receptacle **125** in a manner where air flows through the receptacle **125** as described for example in U.S. Patent 4,338,931 and in U.S. Patent 5,619,985. In another version, the aerosolization of the pharmaceutical formulation may be accomplished by pressurized gas flowing through the inlets, as described for example in US Patent 5,458,135, U.S. Patent 5,785,049, and U.S. Patent 6,257,233, or propellant, as described in PCT Publication WO 00/72904 and U.S, Patent 4,114,615. All of the above references being incorporated herein by reference in their entireties.

In one version, the receptacle **125** comprises a capsule type receptacle. The capsule may be of a suitable shape, size, and material to contain the pharmaceutical formulation and to provide the pharmaceutical formulation in a usable condition. For example, the capsule may comprise a wall **299** which comprises a material that does not adversely react with the pharmaceutical formulation. In addition, the wall may comprise a material that allows the capsule to be opened to allow the pharmaceutical formulation to be aerosolized. In one version, the wall comprises one or more of gelatin, hydroxypropyl methylcellulose (HPMC), polyethyleneglycol-compounded HPMC, hydroxyproplycellulose, agar, or the like. Alternatively or additionally, the capsule wall may comprise a polymeric material, such as polyvinyl chloride (PVC). In one version, the capsule may comprise telescopically ajoined sections, as described for example in U.S. Patent 4,247,066 which is incorporated herein by reference in its entirety. The interior of the capsule may be filled with a suitable amount of the pharmaceutical formulation, and the size of the capsule may be selected to adequately contain a desired amount of the pharmaceutical formulation. The sizes generally range from size 5 to size 000 with the outer diameters ranging from about 4.91 mm to 9.97 mm, the heights ranging from about 11.10 mm to about 26.14 mm, and the volumes ranging from about 0.13 ml to about 1.37 ml, respectively. Suitable capsules are available commercially from, for example, Shionogi Qualicaps Co. in Nara, Japan and Capsugel in Greenwood, South Carolina. After filling, a top portion may be placed over the bottom portion to form the a capsule shape and to contain the powder within the capsule, as described in U.S. Patent 4,846,876, U.S. Patent 6,357,490, and in the PCT application WO 00/07572 published on February 17, 2000, all of which are incorporated herein by reference in their entireties.

In a preferred version, the invention provides a system and method for aerosolizing a pharmaceutical formulation and delivering the pharmaceutical formulation to the respiratory tract of the user, and in particular to the lungs of the user. The pharmaceutical formulation may comprise powdered medicaments, liquid solutions or suspensions, and the like, and may include an active agent.

The active agent described herein includes an agent, drug, compound, composition of matter or mixture thereof which provides some pharmacologic, often beneficial, effect. This

includes foods, food supplements, nutrients, drugs, vaccines, vitamins, and other beneficial agents. As used herein, the terms further include any physiologically or pharmacologically active substance that produces a localized or systemic effect in a patient. An active agent for incorporation in the pharmaceutical formulation described herein may be an inorganic or an organic compound, including, without limitation, drugs which act on: the peripheral nerves, adrenergic receptors, cholinergic receptors, the skeletal muscles, the cardiovascular system, smooth muscles, the blood circulatory system, synoptic sites, neuroeffector junctional sites, endocrine and hormone systems, the immunological system, the reproductive system, the skeletal system, autacoid systems, the alimentary and excretory systems, the histamine system, and the central nervous system. Suitable active agents may be selected from, for example, hypnotics and sedatives, psychic energizers, tranquilizers, respiratory drugs, anticonvulsants, muscle relaxants, antiparkinson agents (dopamine antagnonists), analgesics, anti-inflammatories, antianxiety drugs (anxiolytics), appetite suppressants, antimigraine agents, muscle contractants, anti-infectives (antibiotics, antivirals, antifungals, vaccines) antiarthritics, antimalarials, antiemetics, anepileptics, bronchodilators, cytokines, growth factors, anti-cancer agents, antithrombotic agents, antihypertensives, cardiovascular drugs, antiarrhythmics, antioxicants, anti-asthma agents, hormonal agents including contraceptives, sympathomimetics, diuretics, lipid regulating agents, antiandrogenic agents, antiparasitics, anticoagulants, neoplastics, antineoplastics, hypoglycemics, nutritional agents and supplements, growth supplements, antienteritis agents, vaccines, antibodies, diagnostic agents, and contrasting agents. The active agent, when administered by inhalation, may act locally or systemically.

The active agent may fall into one of a number of structural classes, including but not limited to small molecules, peptides, polypeptides, proteins, polysaccharides, steroids, proteins capable of eliciting physiological effects, nucleotides, oligonucleotides, polynucleotides, fats, electrolytes, and the like.

Examples of active agents suitable for use in this invention include but are not limited to one or more of calcitonin, amphotericin B, erythropoietin (EPO), Factor VIII, Factor IX, ceredase, cerezyme, cyclosporin, granulocyte colony stimulating factor (GCSF), thrombopoietin (TPO), alpha-1 proteinase inhibitor, elcatonin, granulocyte macrophage colony stimulating factor

(GMCSF), growth hormone, human growth hormone (HGH), growth hormone releasing hormone (GHRH), heparin, low molecular weight heparin (LMWH), interferon alpha, interferon beta, interferon gamma, interleukin-1 receptor, interleukin-2, interleukin-1 receptor antagonist, interleukin-3, interleukin-4, interleukin-6, luteinizing hormone releasing hormone (LHRH), factor IX, insulin, pro-insulin, insulin analogues (e.g., mono-acylated insulin as described in U.S. Patent No. 5,922,675, which is incorporated herein by reference in its entirety), amylin, C-peptide, somatostatin, somatostatin analogs including octreotide, vasopressin, follicle stimulating hormone (FSH), insulin-like growth factor (IGF), insulintropin, macrophage colony stimulating factor (M-CSF), nerve growth factor (NGF), tissue growth factors, keratinocyte growth factor (KGF), glial growth factor (GGF), tumor necrosis factor (TNF), endothelial growth factors, parathyroid hormone (PTH), glucagon-like peptide thymosin alpha 1, IIb/IIIa inhibitor, alpha-1 antitrypsin, phosphodiesterase (PDE) compounds, VLA-4 inhibitors, bisphosponates, respiratory syncytial virus antibody, cystic fibrosis transmembrane regulator (CFTR) gene, deoxyreibonuclease (Dnase), bactericidal/permeability increasing protein (BPI), anti-CMV antibody, 13-cis retinoic acid, macrolides such as erythromycin, oleandomycin, troleandomycin, roxithromycin, clarithromycin, davercin, azithromycin, flurithromycin, dirithromycin, josamycin, spiromycin, midecamycin, leucomycin, miocamycin, rokitamycin, andazithromycin, and swinolide A; fluoroquinolones such as ciprofloxacin, ofloxacin, levofloxacin, trovafloxacin, alatrofloxacin, moxifloxicin, norfloxacin, enoxacin, grepafloxacin, gatifloxacin, lomefloxacin, sparfloxacin, temafloxacin, pefloxacin, amifloxacin, fleroxacin, tosufloxacin, prulifloxacin, irloxacin, pazufloxacin, clinafloxacin, and sitafloxacin, aminoglycosides such as gentamicin, netilmicin, paramecin, tobramycin, amikacin, kanamycin, neomycin, and streptomycin, vancomycin, teicoplanin, rampolanin, mideplanin, colistin, daptomycin, gramicidin, colistimethate, polymixins such as polymixin B, capreomycin, bacitracin, penems; penicillins including penicllinase-sensitive agents like penicillin G, penicillin V, penicillinase-resistant agents like methicillin, oxacillin, cloxacillin, dicloxacillin, floxacillin, nafcillin; gram negative microorganism active agents like ampicillin, amoxicillin, and hetacillin, cillin, and galampicillin; antipseudomonal penicillins like carbenicillin, ticarcillin, azlocillin, mezlocillin, and piperacillin; cephalosporins like cefpodoxime, cefprozil, ceftbuten, ceftizoxime, ceftriaxone, cephalothin, cephapirin, cephalexin, cephradrine, cefoxitin, cefamandole, cefazolin, cephaloridine, cefaclor, cefadroxil, cephaloglycin, cefuroxime, ceforanide, cefotaxime, cefatrizine, cephacetrile, cefepime, cefixime, cefonicid, cefoperazone, cefotetan, cefmetazole, ceftazidime,

loracarbef, and moxalactam, monobactams like aztreonam; and carbapenems such as imipenem, meropenem, pentamidine isethiouate, albuterol sulfate, lidocaine, metaproterenol sulfate, beclomethasone diprepionate, triamcinolone acetamide, budesonide acetonide, fluticasone, ipratropium bromide, flunisolide, cromolyn sodium, ergotamine tartrate and where applicable, analogues, agonists, antagonists, inhibitors, and pharmaceutically acceptable salt forms of the above. In reference to peptides and proteins, the invention is intended to encompass synthetic, native, glycosylated, unglycosylated, pegylated forms, and biologically active fragments and analogs thereof.

Active agents for use in the invention further include nucleic acids, as bare nucleic acid molecules, vectors, associated viral particles, plasmid DNA or RNA or other nucleic acid constructions of a type suitable for transfection or transformation of cells, i.e., suitable for gene therapy including antisense. Further, an active agent may comprise live attenuated or killed viruses suitable for use as vaccines. Other useful drugs include those listed within the Physician's Desk Reference (most recent edition).

The amount of active agent in the pharmaceutical formulation will be that amount necessary to deliver a therapeutically effective amount of the active agent per unit dose to achieve the desired result. In practice, this will vary widely depending upon the particular agent, its activity, the severity of the condition to be treated, the patient population, dosing requirements, and the desired therapeutic effect. The composition will generally contain anywhere from about 1% by weight to about 99% by weight active agent, typically from about 2% to about 95% by weight active agent, and more typically from about 5% to 85% by weight active agent, and will also depend upon the relative amounts of additives contained in the composition. The compositions of the invention are particularly useful for active agents that are delivered in doses of from 0.001 mg/day to 100 mg/day, preferably in doses from 0.01 mg/day to 75 mg/day, and more preferably in doses from 0.10 mg/day to 50 mg/day. It is to be understood that more than one active agent may be incorporated into the formulations described herein and that the use of the term "agent" in no way excludes the use of two or more such agents.

The pharmaceutical formulation may comprise a pharmaceutically acceptable

excipient or carrier which may be taken into the lungs with no significant adverse toxicological effects to the subject, and particularly to the lungs of the subject. In addition to the active agent, a pharmaceutical formulation may optionally include one or more pharmaceutical excipients which are suitable for pulmonary administration. These excipients, if present, are generally present in the composition in amounts ranging from about 0.01 % to about 95% percent by weight, preferably from about 0.5 to about 80%, and more preferably from about 1 to about 60% by weight. Preferably, such excipients will, in part, serve to further improve the features of the active agent composition, for example by providing more efficient and reproducible delivery of the active agent, improving the handling characteristics of powders, such as flowability and consistency, and/or facilitating manufacturing and filling of unit dosage forms. In particular, excipient materials can often function to further improve the physical and chemical stability of the active agent, minimize the residual moisture content and hinder moisture uptake, and to enhance particle size, degree of aggregation, particle surface properties, such as rugosity, ease of inhalation, and the targeting of particles to the lung. One or more excipients may also be provided to serve as bulking agents when it is desired to reduce the concentration of active agent in the formulation.

Pharmaceutical excipients and additives useful in the present pharmaceutical formulation include but are not limited to amino acids, peptides, proteins, non-biological polymers, biological polymers, carbohydrates, such as sugars, derivatized sugars such as alditols, aldonic acids, esterified sugars, and sugar polymers, which may be present singly or in combination. Suitable excipients are those provided in WO 96/32096, which is incorporated herein by reference in its entirety. The excipient may have a glass transition temperature (Tg) above about 35° C, preferably above about 40 °C, more preferably above 45° C, most preferably above about 55 °C.

Exemplary protein excipients include albumins such as human serum albumin (HSA), recombinant human albumin (rHA), gelatin, casein, hemoglobin, and the like. Suitable amino acids (outside of the dileucyl-peptides of the invention), which may also function in a buffering capacity, include alanine, glycine, arginine, betaine, histidine, glutamic acid, aspartic acid, cysteine, lysine, leucine, isoleucine, valine, methionine, phenylalanine, aspartame, tyrosine, tryptophan, and the like. Preferred are amino acids and polypeptides that function as dispersing agents. Amino acids falling into this category include hydrophobic amino acids such as leucine,

valine, isoleucine, tryptophan, alanine, methionine, phenylalanine, tyrosine, histidine, and proline. Dispersibility- enhancing peptide excipients include dimers, trimers, tetramers, and pentamers comprising one or more hydrophobic amino acid components such as those described above.

Carbohydrate excipients suitable for use in the invention include, for example, monosaccharides such as fructose, maltose, galactose, glucose, D-mannose, sorbose, and the like; disaccharides, such as lactose, sucrose, trehalose, cellobiose, and the like; polysaccharides, such as raffinose, melezitose, maltodextrins, dextrans, starches, and the like; and alditols, such as mannitol, xylitol, maltitol, lactitol, xylitol sorbitol (glucitol), pyranosyl sorbitol, myoinositol and the like.

The pharmaceutical formulation may also include a buffer or a pH adjusting agent, typically a salt prepared from an organic acid or base. Representative buffers include organic acid salts of citric acid, ascorbic acid, gluconic acid, carbonic acid, tartaric acid, succinic acid, acetic acid, or phthalic acid, Tris, tromethamine hydrochloride, or phosphate buffers.

The pharmaceutical formulation may also include polymeric excipients/additives, e.g., polyvinylpyrrolidones, derivatized celluloses such as hydroxymethylcellulose, hydroxyethylcellulose, and hydroxypropylmethylcellulose, Ficolls (a polymeric sugar), hydroxyethylstarch, dextrates (e.g., cyclodextrins, such as 2-hydroxypropyl-β-cyclodextrin and sulfobutylether-β-cyclodextrin), polyethylene glycols, and pectin.

The pharmaceutical formulation may further include flavoring agents, taste-masking agents, inorganic salts (for example sodium chloride), antimicrobial agents (for example benzalkonium chloride), sweeteners, antioxidants, antistatic agents, surfactants (for example polysorbates such as "TWEEN 20" and "TWEEN 80"), sorbitan esters, lipids (for example phospholipids such as lecithin and other phosphatidylcholines, phosphatidylethanolamines), fatty acids and fatty esters, steroids (for example cholesterol), and chelating agents (for example EDTA, zinc and other such suitable cations). Other pharmaceutical excipients and/or additives suitable for use in the compositions according to the invention are listed in "Remington: The Science & Practice of Pharmacy", 19th ed., Williams & Williams, (1995), and in the "Physician's Desk Reference", 52nd ed., Medical Economics, Montvale, NJ (1998), both of which are incorporated

herein by reference in their entireties.

"Mass median diameter" or "MMD" is a measure of mean particle size, since the powders of the invention are generally polydisperse (i.e., consist of a range of particle sizes). MMD values as reported herein are determined by centrifugal sedimentation, although any number of commonly employed techniques can be used for measuring mean particle size. "Mass median aerodynamic diameter" or "MMAD" is a measure of the aerodynamic size of a dispersed particle. The aerodynamic diameter is used to describe an aerosolized powder in terms of its settling behavior, and is the diameter of a unit density sphere having the same settling velocity, generally in air, as the particle. The aerodynamic diameter encompasses particle shape, density and physical size of a particle. As used herein, MMAD refers to the midpoint or median of the aerodynamic particle size distribution of an aerosolized powder determined by cascade impaction.

In one version, the powdered formulation for use in the present invention includes a dry powder having a particle size selected to permit penetration into the alveoli of the lungs, that is, preferably 10 μm mass median diameter (MMD), preferably less than 7.5 μm, and most preferably less than 5 μm, and usually being in the range of 0.1 μm to 5 μm in diameter. The delivered dose efficiency (DDE) of these powders may be greater than 30%, more preferably greater than 40%, more preferably greater than 50% and most preferably greater than 60% and the aerosol particle size distribution is about 1.0 - 5.0 μm mass median aerodynamic diameter (MMAD), usually 1.5 - 4.5 μm MMAD and preferably 1.5 - 4.0 μm MMAD. These dry powders have a moisture content below about 10% by weight, usually below about 5% by weight, and preferably below about 3% by weight. Such powders are described in WO 95/24183, WO 96/32149, WO 99/16419, and WO 99/16422, all of which are all incorporated herein by reference in their entireties.

Although the present invention has been described in considerable detail with regard to certain preferred versions thereof, other versions are possible, and alterations, permutations and equivalents of the version shown will become apparent to those skilled in the art upon a reading of the specification and study of the drawings. For example, the cooperating components may be reversed or provided in additional or fewer number. Also, the various features of the versions

herein can be combined in various ways to provide additional versions of the present invention. Furthermore, certain terminology has been used for the purposes of descriptive clarity, and not to limit the present invention. Therefore, any appended claims should not be limited to the description of the preferred versions contained herein and should include all such alterations, permutations, and equivalents as fall within the true spirit and scope of the present invention.